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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,449	10/06/2003	Liwen Huang	1438.01	4490

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/680,449	HUANG ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2005 and 09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/4/06* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Interview Summary

An Applicant-initiated interview was held on 4/4/06 to discuss the Final Office Action mailed on 2/22/06 (Interview Summary enclosed herewith; and see Applicant Initiated Interview Request Form filed on 3/28/06). In the interview, Applicants requested a reconsideration and withdrawal of the finality of the Office Action, arguing that the newly applied Written Description and 35 USC 102(b) art rejections could have been applied in the First Office Action and that the newly applied rejections were not necessitated by the amendments to the claims. Applicants further argue that the 102(b) art rejection under Cox et al. does not apply because Cox et al. do not teach non-naturally occurring RNA transcripts, as defined by the specification at page 16. Applicants further argue that Cox et al. do not teach siRNA or shRNA.

While disagreeing with Applicants' assertions regarding the propriety of the finality of the action, the Examiners have agreed to withdraw the finality of the previous Office Action and to consider Applicants' arguments addressing the rejections now of record.

What follows, then, is a Supplemental, Non-Final Office Action, wherein the Examiner has conducted a further search and examination of the instant claims. This Action supersedes the previous Office Action mailed on 2/22/06. That is, the Final Office Action of 2/22/06 is withdrawn in favor of the following Supplemental, Non-Final Office Action.

With this Supplemental, Non-Final Office Action, the Examiner has conducted an additional search of the prior art patent and non-patent literature, updating the previous searches to once again examine the claims with regard to utility, novelty, obviousness, written description, and enablement.

Applicants are reminded that 37 CFR §1.111(b) requires that "In order to be entitled to reconsideration or further examination, the applicant or patent owner must reply to the Office action. The reply by the applicant or patent owner must be reduced to a writing which distinctly and specifically points out the supposed errors in the examiner's action and must reply to every ground of objection and rejection in the prior Office action."

Furthermore 37 CFR § 1.2 (Business to be transacted in writing) requires that "All business with the Patent and Trademark Office should be transacted in writing."

While arguments may be heard by interview, full consideration and weight will be given only to those arguments and facts presented in writing to this Office Action. Accordingly, the rejections of record are maintained until such time as Applicants respond to all rejections in writing.

Copies of the non-patent literature cited herein were provided to Applicants with the previous Office Action.

Amendments/ Status of the Application

Claims 1–34 are pending. Claims 1-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants' amendments to claims 16 and 18 and submission of new claims 21–34 are acknowledged. Also acknowledged are Applicants amendments to page 65 of the specification, filed on 11/9/05. As requested the amendments have been entered into the application.

Applicant's responses filed 11/9/05 and 12/9/05 have been considered. The following Final Office Action is offered in reply. Rejections and/or objections not reiterated from the previous Office Action mailed on Aug. 9, 2005, are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30 and 34 contain the trademark/trade name "FLAG". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to

identify/describe a detectable peptide tag and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16–34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn generally to kits comprising a plurality of expression vectors, cells, or organisms expressing chimeric RNA transcripts having different subject RNAs operably

linked with the same "universal target RNA"; and a universal interfering RNA targeting said universal target RNA or an interfering RNA transcription vector that directs the expression of said universal interfering RNA, wherein said universal interfering RNA is an siRNA or shRNA. Claims 27–34 further limit the claims by stating that the chimeric RNA transcripts encode fusion proteins, having first and second amino acid sequences, wherein the second amino acid sequence is a detectable peptide tag.

The terms "subject RNA" and universal target RNA" are defined by the specification as follows:

"The term "subject RNA," as used herein, refers to an (RNA whose cellular concentration is to be altered, manipulated or reduced, or knocked down, by the action of an interfering RNA targeting the universal target RNA, but not the subject RNA." (page 16)

The term "universal target RNA," or UtRNA, as used herein, refers to a common RNA that is incorporated into a plurality of chimeric RNA transcripts, and serves to impart upon the chimeric RNA transcripts a susceptibility to degradation by RNA interference promoted by a "universal interfering RNA" targeting the universal target RNA." (page 17)

Thus, the claims are extremely broad, encompassing any siRNA or shRNA targeting any UtRNA operably linked to any subject RNA in any vector, in any cell, or in any organism.

Adequate written description does not exist in the instant application for all these kits. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of universal interfering siRNAs, shRNAs, and expression vectors expressing said siRNAs and shRNAs targeting all possible universal target RNAs, including those that code for all possible detectable peptide tags

such as those recited in claims 30 and 34, as now claimed in the instant claims. The instant application does not enable the skilled artisan to envision the structure of all possible siRNAs and shRNAs needed to target all possible universal target RNAs including all such target RNAs that code for detectable peptide tags.

MPEP §2163 states that "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed (See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 [Fed. Cir. 2004])"

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that, as of the effective filing date, Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the detailed chemical structure of the encompassed genus of universal interfering siRNAs and shRNAs targeting the entire genus of universal target RNAs.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures,

diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The instant application provides general guidance and two prophetic examples (pages 76–78) directed to the instantly claimed universal siRNAs and shRNAs. However, the disclosure is largely directed to the function of these siRNAs and shRNAs and does not convey with reasonable clarity the essential physical characteristics of the siRNAs and shRNAs themselves. In fact, the examples and the specification as a whole do little more than outline goals that might be achieved with the instantly claimed kits. Neither the instant application nor the prior art provide a well established correlation between the structure of the recited universal siRNAs, shRNAs and their function.

Describing an invention by its function alone is little more than a wish for possession; it does not satisfy the written description requirement. Furthermore, the fact that one of skill in the art could determine the structure of the claimed "universal interfering" siRNAs and shRNAs for any "unversal target RNA" by screening and assaying for such siRNAs using conventional techniques is not the standard; what is needed is a description of the siRNAs and shRNAs themselves. The lack of written descrtiption is heightened by the fact that the specification provides no specific, defined target sequence of any "universal target RNA," which sequence might serve to describe the siRNAs that may be used to target such sequence. While specific peptide-encoding sequences are contemplated and claimed for use in the claimed "chimeric" constructs, Applicants provide no identifiable nucleotide sequence or core structure of such sequences from which to derive possible universal siRNA or shRNA compounds. Essentially, Applicants are claiming any siRNA or shRNA targeting any nucleic acid sequence encoding any

detectable peptide tag, which may be any of those recited in the instant claim or, in fact, any sequence detectable by any method.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

In the instant case, both the prior art and the instant application indicate a significant degree of unpredictability in the art as it relates to the genus of claimed siRNAs and shRNAs. In fact, the Applicants themselves acknowledge the inability of an investigator or one of skill in the art to identify or select an siRNA for gene expression inhibition *a priori* based on a complementary sequence. This general affirmation would apply to any sequence, including any universal target sequence, as now claimed.

For example, the instant application states at pages 4–5:

> "Unfortunately, once a gene is selected for siRNA-induced silencing, the choice of which sequences to target by siRNAs is somewhat unclear. Towards this end, Holen and colleagues investigated the efficacy of siRNAs targeted to 30 different positions in the transcript of human coagulation trigger Tissue Factor (hTF) in a variety of human cell types in culture (See Holen et al., Nucleic Acids Res. 30:1757-1766 [2002]). (2002)). In this study several siRNAs corresponding to several target sequences located in hTF transcripts were synthesized and tested for their ability to induce silencing of the hTF gene. Of the several siRNAs synthesized and tested only a few resulted in a significant reduction in expression of hTF, suggesting that accessible siRNA target sites may be rare in some human mRNAs. Further, siRNAs targeting different sites in the hTF mRNA demonstrated striking differences in their ability to silence the expression of hTF. Although, strong positional effects were seen with the siRNAs tested, and regions of high GC content seem to be targeted less efficiently than those of low GC content, Holen and

coworkers concluded that the factors determining the differences in siRNA efficiency remain unclear, and that susceptible RNAi target sites in some human genes may be rare."

"From a practical perspective, the results of Holen and colleagues suggest that it is difficult, if not impossible to predict, *a priori*, what sequences to target in a gene to target with siRNAs to induce efficient silencing by RNAi. In addition, there is a growing body of evidence that specific siRNAs selected to silence particular genes may produce unwanted and unanticipated off-target effects—altering the expression of untargeted RNA transcripts." (bold underline added)

At page 4 the specification states further that

"Unfortunately, once a gene is selected for siRNA-induced silencing, the choice of which sequences to target by siRNAs is somewhat unclear."

At page 5, the specification states that

"They [Jackson and colleagues] conclude that it may be difficult to select an siRNA sequence that will be absolutely specific for the target of interest."

And at page 7, the specification states

" Despite numerous studies in which siRNAs have been employed to induce gene silencing, no definitive rules have evolved to assist researchers in picking the most effective sequences to target within a given transcript."

Thus, according to the specification and the prior art (Holen et al. [2002] *Nucleic Acids Res.* 30:1757-1766), it is difficult if not impossible to predict the structure of siRNAs that induce efficient gene silencing. The Examiner submits that this same limitation applies to the instantly claimed "universal interfering RNAs." A universal interfering siRNA, for example, required to target a particular universal target RNA, would be bound by the same rules and biochemical limitations of any other siRNA targeting any other mRNA transcript, whether the transcript is "chimeric" or not. Yet the instant application does not describe even a single exemplary interfering siRNA for any particular universal target RNA in any chimeric RNA transcript.

In fact, the prior- and post-filing art is replete with reports documenting the variability in the genus of siRNA and shRNAs.

Brown et al. (US 2004/0029275 A1) state at paragraph 14 that "Not all dsRNA or candidate siRNA molecules can effect RNA interference of a target gene." "To date the design of an effective siRNA is determined empirically, which requires time and labor for screening and verification of RNAi activity."

On top of the variability with regard to the structure/function relationship of siRNAs and shRNAs is the necessity of the claimed siRNAs and shRNAs to mediate degradation not just of the local sequence targeted, but of an entire "chimeric" mRNA transcript such that no functional proteins are produced (see Applicants' asserted utility at page 10), The Examiner submits that it cannot be predicted *a priori* that any given universal interfering siRNA or shRNA targeting any universal target RNA, such as an RNA encoding a detectable peptide tag at the 3' end for example (see Fig. 1) will cause partial or complete degradation and inhibition of expression of the corresponding plurality of operably linked subject RNAs since the post-filing art teaches that

> "In addition, single siRNAs cause cleavage of the target mRNA at a single site, opening the possibility that the remaining 3'-fragment will be translated. The resulting N-terminal truncated protein may act as a dominant negative or constitutively active protein rather than as a true protein-null." (Myers et al., US Patent Application Publication 2003/0224432, paragraph 6)

Thus, this teaching adds a further layer of unpredictability regarding the correlation between the structure and function of the claimed genus of universal interfering siRNAs, indicating that cleavage of the mRNA at the extreme 3' end will not necessarily always prevent translation of a protein product, having some unknown or aberrant function.

In view of the unpredictability in the art, the skilled artisan would need to look to the specification for guidance as to the structure of such siRNAs for targeting universal target RNAs operably linked to different subject RNAs; however no guidance is given.

The prior art clearly teaches methods for synthesizing candidate siRNAs; however the prior art and the instant application also recognize the need for empirical, trial and error testing to definitively establish siRNA function *in vitro* and *in vivo.* The instant application expressly states on page 7:

> "Despite numerous studies in which siRNAs have been employed to induce gene silencing, no definitive rules have evolved to assist researchers in picking the most effective sequences to target within a given transcript. Although there are general guidelines to help researchers narrow their choices for target sequences, researchers must still use a trial and error approach to empirically determine what individual siRNAs work best, and what siRNAs have minimal off-target effects."

Without providing specific guidance as to the chemical/physical structure of even a single exemplary universal interfering siRNA, how, then, does the instant application enable the skilled artisan to envision the structure of all possible universal interfering siRNAs targeting every conceivable universal target RNA, as now claimed in claims 16 and 18, for example?

In sum, the prior art and the instant application indicates a fair degree of variability in the genus of universal interfering siRNAs and shRNAs. The term "siRNA" stands for short interfering RNA. The claimed component is, therefore, recited very broadly in terms of its function, not any particular structure, nor have applicants suggested or taught any specific structure or class of structures defining either the siRNAs or the universal targets themselves. Thus, with regard to the broad genus now claimed, neither the prior art nor the instant application has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention

from a recitation of its function. Furthermore, the instant application does not describe a representative number of species that would reasonably correlate with the claimed genus such that the skilled artisan would recognized that applicants were in possession of the entire genus of universal targeting siRNA at the time the instant application was filed.

MPEP §2163.05, Section II, 3, a, ii, states in part that

> "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406."
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.").

Neither of these criteria are fulfilled by the instant application.

In view of the breadth of the instant claims, it must be concluded that the instant application fails to describe the full scope of the instantly claimed inventions in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the entire genus of universal interfering siRNAs and shRNAs, as currently claimed, for targeting the entire genus of universal target RNAs.

Accordingly, the instant claims are rejected for failing to meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Response to Arguments—Claim Rejections - 35 USC § 102

The rejection of record under Cox et al. is hereby withdrawn in view of Applicants' definition of "chimeric RNA transcript" at page 16 of the specification, which excludes naturally occuring transcripts such as those targeted by Cox et al.

Response to Applicants' Arguments

Applicants' arguments presented on 11/9/05 and 12/9/05 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Louis Wollenberger
Examiner, Art Unit 1635
May 12, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635